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EXAMINER	
GUDIBANDE, SATYANARAYAN R	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
10/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/502,065	LAUTT ET AL.	
	Examiner	Art Unit	
	SATYANARAYANA R. GUDIBANDE	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-18,21-25 and 29-31* is/are pending in the application.

4a) Of the above claim(s) *7,18,22,29 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,8-17,21-25 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/30/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group II invention (claims 6, 8, 11, 29 and 30) and election of N-acetylcysteine and SIN-1 as species in the reply filed on 8/11/06 was acknowledged and the traversal arguments were answered in the office action dated 9/11/06.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/30/08 has been entered.

Claims 6-18, 21-25 and 29-31 are pending.

Claims 7, 18, 22, 29 and 30 and have been withdrawn from further consideration as being drawn to non-elected species.

Claims 6, 8-17, 21-25 and 31 are examined on the merit.

Any objections and/or rejections made in the previous office action dated 12/28/07 and not specifically mentioned here are considered withdrawn.

Withdrawn Rejections

Claim Rejections - 35 USC § 102

Applicant's arguments, see pages 6-8, filed 6/30/08, with respect to the rejection(s) of claim(s) 6 and 8 under 35 USC 102(b) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of recently found prior art.

Claim Rejections - 35 USC § 103

Applicant's arguments, see pages 8-9, filed 6/30/08, with respect to the rejection(s) of claim(s) 6, 8-17, 21-23, 24(in part to the extent that it reads on non-insulin dependent diabetes), 25 and 31 under 35 USC 103(a) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of recently found prior art.

New grounds of Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 6, 8-17, 21-25 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the instant application, applicants claim a pharmaceutical composition comprising a therapeutically effective amount of hepatic glutathione increasing compound and a therapeutically effective amount of hepatic nitric oxide donor compound for reducing insulin resistance.

Factors to be considered in making the determination as to whether one skilled in the art would recognize that the applicant was in possession of the claimed invention as a whole at the time of filing include:

a. Actual reduction to practice;

b. Disclosure of drawings or structural chemical formulas;

c. Sufficient relevant identifying characteristics such as:

i. Complete structure,

ii. Partial structure,

iii. Physical and/or chemical properties or

iv. Functional characteristics when coupled with a known or disclosed correlation between function and structure;

d. Method of making the claimed invention;

e. Level of skill and knowledge in the art, and

f. Predictability in the art.

While all of these factors are considered, a sufficient number for a *prima facie* case are discussed below with a primary focus on the correlation between structure and function of the hepatic glutathione increasing compounds and hepatic nitric oxide donors.

Claim 6 as recited provides only a functional definition for the constituents of the pharmaceutical composition as "hepatic glutathione increasing compound" and "hepatic nitric oxide donors". The claim as recited does not provide a chemical structure for the "hepatic glutathione increasing compound" and "hepatic nitric oxide donors". The claim does not provide the nature of physical or chemical properties of the molecule that is responsible for the molecule to possess the desired functions of "glutathione increasing compound" and NO donor". The specification provide a non-limiting definition for the hepatic glutathione increasing compound as, "[F]or example, hepatic glutathione may be increased by increasing the rate of glutathione synthesis in the liver, reducing the rate of glutathione degradation (other than to form HISS) in the liver, or by providing exogenous glutathione in a form which is taken up by the liver cells. By way of non-limiting example, the rate of glutathione synthesis in the liver may in some instances be increased using one or more compounds: (a) which stimulate enzymes involved in glutathione synthesis (but the compounds are not reactants in the reactions producing glutathione); (b) which are reactants in the reaction producing glutathione; or (c) which stimulate the production of one or more subsequent compounds which either stimulate glutathione producing enzymes or are reactants in the reaction producing glutathione. In light of the disclosure herein, one skilled in the art could select a suitable method of increasing hepatic glutathione. Examples of glutathione-increasing compounds include: n-acetylcysteine, cysteine esters, L-2-oxothiazolidine-4-carboxolate ("OTC"), gamma glutamylcysteine and its ethyl ester,

glutathione ethyl ester, glutathione isopropyl ester, lipoic acid, cystine, cysteine, methionine, and s-adenosylmethionine". Although, the specification includes several specific compounds as examples, the claim as recited encompasses any and all compounds known and unknown structural features that are remotely connected to glutathione synthesis in liver cells.

With respect to "NO donors", the claim recites "a therapeutically effective amount of hepatic nitric oxide donors". By the presentation of the claim reciting "donors", it implies more than one 'nitric oxide donor' is present in the composition. The instant specification provides the following definition for 'NO donor': "hepatic NO levels can be increased by increasing the rate of NO synthesis in the liver (such as by increasing NO synthase activity), by reducing the rate of NO degradation in the liver (other than to form HISS), or by providing exogenous NO or an exogenous carrier or precursor which is taken up and releases NO in the liver. NO-increasing compounds include SIN-1 and molsidamine, and nitrosylated forms of: N-acetylcysteine, cysteine esters, L-2-oxothiazolidine-4-carboxolate ("OTC"), gamma glutamylcysteine and its ethyl ester, glutathione ethyl ester, glutathione isopropyl ester, lipoic acid, cystine, cysteine, methionine, and s-adenosylmethionine. When nitrosylated forms of glutathione-increasing compounds are administered, these compounds can perform the role of both a nitric oxide-increasing compound and a glutathione-increasing compound". Although, the specification includes several specific compounds as examples, the claim as recited encompasses any and all combinations of compounds of both known and unknown structural features that are remotely connected to nitric oxide donors in liver. Moreover, the lists for 'glutathione increasing compounds" and "NO donors" include the same compounds, thus embracing all known and unknown compounds that can perform both functions simultaneously. Hence the claim as recited

requiring "a glutathione increasing compound" and "NO donors" may be accomplished by administration of one compound whose structure, physical and chemical properties are not apparent from the claim as recited.

The prior art of Corrales, 1999, Journal of Hepatology, 31, 887-894, discloses administration of buthionine sulfoximine (BSO) and glutathione monoethylester (EGSH) administered to regulate the hepatic methionine adenosyltransferase enzyme. Compared to the instant invention, the cited prior art discloses specific compounds in the composition.

Thus the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 6 and 8 rejected under 35 U.S.C. 102(b) as being anticipated by Buckley, 2000, Am. J. Physiol. Cell Physiol, 279, C1168-C1176.

In the instant application, applicants claim a pharmaceutical composition comprising a therapeutically effective amount of hepatic glutathione increasing compound and a therapeutically effective amount of hepatic nitric oxide donor compound for reducing insulin resistance.

The claim as recited is drawn to a composition that comprises a hepatic glutathione increasing compound and a hepatic nitric oxide donor. The claim as recited implies that if the composition comprises a compound that is a nitric oxide donor and that by itself increases the glutathione level in vivo upon administration, it meets the limitation of the instant claim.

Buckley discloses that the endothelial cells (EC) were treated with SIN-1 and it resulted in increase in glutathione levels in the cells (figure 1 on page C1169 and figure 10 on page C1173) and resulted in an increase of glutathione in smooth muscle cells (SMC) (figure 5 on page C1171). This reads on instant claim 1.

Buckley further discloses the effect of SIN-1 on cysteine uptake in endothelial cells (EC) and smooth muscle cells (SMC). The cells were treated with SIN-1 and after 19 hours the cells were washed and incubated with HEPES buffer containing 600 μM Cysteine (figure 6 on page C1171 and figure 10 on page C1173). The claims as recited is drawn using the transition phrase "comprising" and hence the composition does not have to contain the glutathione increasing compound and the nitric oxide donor and administered at the same time. The treatment of cells with SIN-1 followed by cysteine meets the limitations of claim 6. The cysteine being a reducing amino acid is an antioxidant, the introduction of the cysteine to the cells reads on instant claim 8. Also, the instant specification does not define the phrase "therapeutically effective amount" by providing a dosage amount that would constitute a therapeutically an effective amount. Since Buckley discloses treating cells with SIN-1 and cysteine in 10 mM HEPES buffer wherein it increases the glutathione levels, it is inherent that it reduces insulin resistance and hence it meets the limitation of a pharmaceutical composition and hence reads on instant claims 6 and 8.

Hence claims 6 and 8 are anticipated by the cited reference of Buckley.

Claims 6 and 8 rejected under 35 U.S.C. 102(b) as being anticipated by Corrales, 1999, Journal of Hepatology, 31, 887-894.

In the instant application, applicants claim a pharmaceutical composition comprising a therapeutically effective amount of hepatic glutathione increasing compound and a therapeutically effective amount of hepatic nitric oxide donor compound for reducing insulin resistance.

Corrales discloses administration of D,L-Buthione S,R-sulfoximine (BSO) glutathione monoethylester (EGSH) to rat liver via intraperitonial injection (figure 5 on page 890). The reference discloses that BSO as a nitrosylating agent (NO donor) and EGSH as a permeable derivative of glutathione (GSH) (Abstract). Since the compounds are administered to rat liver intra-peritoneally, the composition must be in a pharmaceutical composition. Also, the instant specification does not define the phrase "therapeutically effective amount" by providing a dosage amount that would constitute a therapeutically an effective amount. This reads on instant claim 6. The reference also teaches that simultaneous administration of BSO and EGSH prevented the effect of BSO i. e., lowering of hepatic GSH level (page 891, bridging paragraph between columns 1 and 2). The reference also teaches that SIN-1(elected species) as a nitric oxide donor (page 891, column 2, paragraph 1). The EGSH is a precursor for the glutathione and is an anti-oxidant and hence composition comprising EGSH reads on the limitation instant claim 8.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9-17, 21-25 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Corrales as applied to claim 6 and 8 above, in view of WO 00/19992 of Lautt and further in view of Mattia, 1998, Diabetooglia, 41, 1392-1396.

In the instant application, applicants claim a pharmaceutical composition comprising a therapeutically effective amount of hepatic glutathione increasing compound and a therapeutically effective amount of hepatic nitric oxide donor compound for reducing insulin resistance.

The reference of Corrales did not teach the N-acetyl cysteine in the pharmaceutical composition to reduce insulin resistance.

The reference of Corrales, discloses a condition of reduced glutathione level in BSO induced rat. The reference also teaches that BSO and EGSH administered to regulate the hepatic methionine adenosyltransferase enzyme (Abstract).

The reference of Lautt discloses composition comprising a nitric oxide donor SIN-1 and a method to increase insulin sensitivity and hence reducing insulin resistance. The composition is administered to treating obesity, insulin resistance and diseases associated with insulin resistance in patients (page 8, lines 3-30). This reads on instant claims 6, 10, 12, 15, 21, 24 and 31. The reference also teaches that the composition can be administered in various ways including oral and intravenous delivery and to humans (page 12, lines 4-23). This reads on instant claims 16, 17 and 25. The reference further teaches that the composition comprises various vehicles, adjuvants and carriers such as liposomes, polymers, antibodies, etc. This reads on instant claims 11 and 29. Rapid insulin sensitivity test (RIST) index is a measure to express insulin sensitivity as the total amount of glucose mg/kg infused over 30 minutes after insulin administration. The reference teaches that RIST after denervation and intraportal SIN-1 significantly reduced the RIST index from 208 mg/kg to 87 mg/kg. Hence administration of SIN-1 improves glucose uptake (page 23, lines 9-15). This reads on instant claim 31.

Mattia, et al., have shown that administration of N-acetylcysteine in non-insulin diabetic patients increases the glutathione and GSH/GSSG ratio concentration in non-insulin dependent diabetic patients (column 2 of 'summary' on page 1392). This reads on instant claims 6, 13, 14 and 24. Since N-acetylcysteine increases the GSH levels, it is an antioxidant and hence reads on instant claims 8 and 23.

It would have been obvious to one of ordinary skill in the art to combine the references of Corrales, Lautt and Mattia to arrive at the instant invention. Because, Corrales discloses pharmaceutical composition of BSO (a NO donor) and EGSH (a glutathione increasing compound), Lautt discloses the composition and method for reducing insulin resistance in a mammal by administration of SIN-1 and the reference of Mattia discloses the composition comprising N-acetyl cysteine to treat non-insulin dependent diabetes. It would have been obvious to one of ordinary skill in the art to use a combination of elected species SIN-1 (NO donor) and a N-acetyl cysteine (glutathione increasing compound) in a composition because such a composition as taught by Corrales and each of the two individual species were taught by Lautt and Mattia to reduce insulin resistance. One would have been motivated to do given the fact Corrales used the composition to increase the in vivo concentration of GSH in rat liver.

Also, as set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980), "It is *prima facie* obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; the idea of combining them flows logically from their having been individually taught in prior art." In this case SIN-1 and N-acetyl cysteine are used in the composition for reducing the insulin resistance. As afore-described each of these compounds have been known to reduce insulin resistance as taught by Lautt and Mattia. Hence according to *In re Kerkhoven*, the idea of combining two compounds in a composition logically flows as they have been known to posses the property of reducing insulin resistance individually in prior art.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12

USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Satyanarayana R Gudibande/
Examiner, Art Unit 1654

/Andrew D Kosar/
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